UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,775	09/17/2003	Ruth Buemann Simesen	6448.200-US	5501

23650 7590 08/26/2004

NOVO NORDISK PHARMACEUTICALS, INC
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

EXAMINER	
DESAI, ANAND U	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/664,775	SIMESEN ET AL.	
	Examiner	Art Unit	
	Anand U Desai, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *28* is/are allowed.

6)☒ Claim(s) *1-27 and 29-41* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/14/03& 5/28/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. The priority date is September 20, 2002.

Oath/Declaration

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). The oath filed on January 20, 2004 has an alteration without an initial or date next to the alteration, where Inventor 4 signed the oath in the area designated for Inventor 2 and changed the number 2 to 4.

Specification

3. The disclosure is objected to because of the following informalities:

4. On pae 12, line 32, there is a space missing between the primer identifier, CLC56L and the primer sequence (SEQ ID NO: 10).

5. The use of the trademark "FUGENE 6" has been noted in this application on page 15, line 14. The use of the trademark "GENEJAMMER" has been noted in this application on page 16, line 7. The trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Appropriate correction is required.

Claim Objections

6. Claim 1 is objected to because of the following informality: The words scaffold/matrix attachment region should be spelled out in the first occurrence along with the designation S/MAR. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 3, 4, 15, 16-27, and 30-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. In claims 3, 4, and 16 the phrase "at least about" is indefinite. The lower limit is not clearly defined?

10. In claims 3, and 16, the phrase "70 % homologous" is indefinite. Does applicant intend to describe a sequence with 70% identity? It is not clear what sequences are encompassed in the claims?

11. In claims 15, and 30 the phrase "less than about" is indefinite. The lower limit is not clearly defined?

12. In claims 36, and 39 the phrase, "expression control elements" is indefinite. What is meant by "expression control elements?" Would a S/MAR be an "expression control element?"

13. In claim 41, the phrase "consisting essentially of" is indefinite. Suggest using the word comprising.

14. Claims 17-27 are rejected for depending on a rejected claim 16.

15. Claims 31-35 are rejected for depending on a rejected claim 30.

16. Claims 37, and 38 are rejected for depending on rejected claim 36.

17. Claim 40 is rejected for depending on rejected claim 39.

18. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 1-27, and 29-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification does not teach a "functional fragment" of scaffold/matrix attachment region and having the activity of a regulatory element. Therefore, these designated terms lack written description in claims 3, 4, and 16. The specification does not clearly define "functional analogue" of a human protein or polypeptide as claimed in claim 29.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a

precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at *23, quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). Thus the phrases, "functional fragment" in claims 3, 4, and 16, "functional analogue" in claim 29 lacks adequate written description. Claims 5-15, 17-27, and 30-40 are rejected for depending on a rejected claim.

20. Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing Factor VII by transfecting a mammalian cell with a nucleic acid molecule comprising a scaffold/matrix attachment region identified by SEQ ID NO: 1-5, does not reasonably provide enablement for producing Factor VII by transfecting a mammalian cell with a nucleic acid molecule comprising any scaffold/matrix attachment region. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) eight factors should be addressed in determining enablement.

1.) The nature of the invention: the invention is drawn method for producing a polypeptide by transfecting a mammalian cell with a nucleic acid molecule comprising a sequence encoding a polypeptide, and at least one scaffold/matrix attachment region; culturing the mammalian cell for expression and isolating the expressed polypeptide.

2.) The breadth of the claims: the claims are broad in that any mammalian cell can be transfected with a nucleic acid molecule comprising any scaffold/matrix attachment sequence.

3.) The predictability or unpredictability of the art: there is unpredictability in the art when cells are transfected with nucleic acid molecules comprising scaffold attachment regions. Poljak et al. (Nucleic Acid Research 22(21) : 4386-4394 (1994)) has described differences of expression levels of chloramphenicol acetyltransferase when a vector contains a minimal Drosophila scaffold attachment region. The expression level of chloramphenicol acetyltransferase fails to normalize to a consistent value (see Figure 2, A and B pp. 4389 and 2nd paragraph of Discussion section pp. 4393).

4. & 5.) The amount of direction or guidance presented, and the presence or absence of working examples: The amount of guidance for Factor VII production in examples 3 to 7 would not invariably result in expression of any polypeptide with any scaffold/matrix attachment region in any mammalian cell.

6.) The quantity of experimentation necessary: There is a large quantity of experimentation necessary to determine the method of producing any polypeptide in any mammalian cell using a nucleic acid molecule comprising any scaffold/matrix attachment region sequence. Blasquez et al. (Journal of Biological Chemistry, 264(35): 21183-21189 (1989)) describes the importance of integrated transformants as compared to transient transfection of mammalian cells when using constructs comprising scaffold/matrix attachment regions. Studies employing transient transfection of mammalian cells failed to detect a function for the matrix attachment region (see pp. 21183, 3rd paragraph of Introduction).

7.) The state of the prior art: The nuclear matrix was regarded as a static structure. It was thought to arrange chromatin into transcriptional domains, by providing a place for the transcriptional machinery and active genes to intermingle. In some cases these anchors can also function to shield specific domains from neighboring enhancers and the silencing effects of heterochromatin. The exact nature of the association of the nuclear matrix with DNA remains to be fully characterized (see Ostermeier et al. Nucleic Acid Research 31(12): 3257-3266 (2003), particularly 2nd paragraph of Introduction).

8.) In view of the discussion of each of the preceding seven factors the level of skill in this art is high and is at least that of a doctoral scientist with several years of experience in the art. As the cited art would point to, even with a level of skill in the art which is of a doctoral scientist, predictability of the results in not invariable. In consideration of each of factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC § 102

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

22. Claims 16-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Delcuve (U.S. Patent 5,888,774). Delcuve discloses a method of expressing recombinant mammalian

erythropoietin comprising the steps of culturing a mammalian cell transformed with a vector comprising a nucleic acid molecule encoding a mammalian erythropoietin, an expression control sequence operatively linked to at least one human apolipoprotein B scaffold attachment region element and separating the erythropoietin produced. The nucleic acid molecule encoding mammalian erythropoietin and the expression control sequence operatively linked thereto are flanked by scaffold attachment region elements. Delcuve found that vectors with scaffold attachment regions have increased expression of erythropoietin compared to vectors without scaffold attachment sequences (see U.S. Patent '774, column 3, lines 28-45, and claims 1, 6, 7, 10, 11, 12, and 13, current application, claims 16-18).

Claim Rejections - 35 USC § 103

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

24. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

25. Claims 1-5, 15-18, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Delcuve (U.S. Patent 5,888,774) in view of Hagen et al. (U.S. Patent 4,784,950). Delcuve discloses a method of expressing recombinant mammalian erythropoietin comprising the steps of culturing a mammalian cell transformed with a vector comprising a nucleic acid molecule encoding a mammalian erythropoietin, an expression control sequence operatively linked to at least one human apolipoprotein B scaffold attachment region element and separating the erythropoietin produced. The nucleic acid molecule encoding mammalian erythropoietin and the expression control sequence operatively linked thereto are flanked by scaffold attachment region elements (see U.S. Patent '774, column 3, lines 28-45, and claims 1, 6, 7, 10, 11, 12, and 13, current application, claims 16-18). Delcuve does not disclose the method for recombinant expression of Factor VII or a Factor VII-related polypeptide. Hagen et al. claims a method of producing recombinant Factor VII, transforming a mammalian host cell with a DNA plasmid comprising a promoter, a sequence encoding Factor VII, and a downstream polyadenylation signal (see U.S. Patent '950, claims 13, and 24). One would have been motivated to produce FVII as a treatment for patients with coagulation disorders. Because Delcuve found that vectors with scaffold attachment regions have increased expression of recombinant erythropoietin compared to vectors without scaffold attachment sequences one would have been motivated to express increased amounts of Factor VII using a vector containing a scaffold/matrix attachment region. Therefore, it would have been obvious to the person having ordinary skill in the art to produce and isolate a Factor VII or Factor VII-related polypeptide to treat patients with coagulation disorders, by culturing a mammalian cell which has been transfected with a nucleic acid molecule comprising a sequence encoding Factor VII or a Factor VII-related polypeptide,

and a scaffold attachment region nucleic acid sequence to increase the expression of Factor VII or a Factor VII-related polypeptide (current application, claims 1-5, 15-18, and 36).

Conclusion

26. Claim 28 is allowable.

27. Claims 1-27, and 29-41 are not allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 9:00 a.m. - 5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (517) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen Cochrane Carlson PhD

***
August 23, 2004

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER